STN

FILE 'HOME' ENTERED AT 12:43:37 ON 14 JUL 2005

L1 206 (HPV OR PAPILLOMA?) AND (PDZ OR DLG OR MAGUK OR MAGI### OR MEMBR ANE (A) ASSOCIATED (A) GUANYLATE (A) KINASE (A) INTERACTING (A) PROTEIN?)

L2 176 L1 AND "E6" (P) (PDZ OR DLG OR MAGUK OR MAGI### OR MEMBR ANE (A) ASSOCIATED (A) GUANYLATE (A) KINASE (A) INTERACTING (A) PROTEIN?)

L3 44 L1 AND "E6" (S) PDZ (P) (MAGI### OR MEMBRANE (A) ASSOCIATED (A) GUANYLATE (A) KINASE (A) INTERACTING (A) PROTEIN?)

(FILE 'HOME' ENTERED AT 12:43:37 ON 14 JUL 2005)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, CANCERLIT' ENTERED AT 12:44:14 ON 14 JUL 2005

L1 206 S (HPV OR PAPILLOMA?) AND (PDZ OR DLG OR MAGUK OR MAGI### OR ME
L2 176 S L1 AND "E6" (P) (PDZ OR DLG OR MAGUK OR MAGI### OR MEMBR
L3 44 S L1 AND "E6" (S) PDZ (P) (MAGI### OR MEMBRANE (A) ASSOCIATED (
L4 104 S L2 AND PY<2003
L5 23 S L4 AND L3
L6 4 DUP REM L5 (19 DUPLICATES REMOVED)
L7 23 DUP REM L4 (81 DUPLICATES REMOVED)
L8 19 S L7 NOT L6

L6 ANSWER 1 OF 4 MEDLINE on STN DUPLICATE 1
AN 2002683177 MEDLINE
DN PubMed ID: 12444549
TI Chimaeric **HPV** E6 proteins allow dissection of the proteolytic pathways regulating different E6 cellular target proteins.
AU Pim David; Thomas Miranda; Banks Lawrence
CS International Centre for Genetic Engineering and Biotechnology, Area Science Park, Padriciano-99, I-34012, Trieste, Italy.. pim@icgeb.org.it
SO Oncogene, **(2002 Nov 21)** 21 (53) 8140-8.
Journal code: 8711562. ISSN: 0950-9232.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200212
ED Entered STN: 20021122
Last Updated on STN: 20021227
Entered Medline: 20021223
AB The ability of **HPV E6** oncoproteins to induce the degradation of **PDZ** domain-containing **MAGUK** proteins correlates with their malignant potential. We previously showed that the **HPV**-6 **E6** protein, when provided with the **PDZ** -binding domain from **HPV**-18 **E6**, acquires the ability to bind the Discs Large (**Dlg**) tumour suppressor and target it for degradation. Based on this finding we have extended this analysis to **E6** proteins from a variety of different **papillomavirus** types. Cloning a **PDZ**-binding sequence onto the C-terminus of **E6** proteins derived from low-risk mucosal, and low and high-risk cutaneous **papillomavirus** types, enables them to bind **Dlg** and a second **MAGUK** family member, **MAGI**-1. This renders the mucosally-derived low-risk chimaeric **HPV E6** proteins capable of targeting **Dlg** for degradation, but they are unable to induce significant levels of degradation of **MAGI**-1. In contrast, none of the **E6** proteins derived from cutaneous **papillomavirus** types induce significant degradation of either **MAGI**-1 or **Dlg** when provided with a **PDZ**-binding domain. These results demonstrate significant differences, both between mucosal and cutaneous **HPV E6** proteins and in the pathways required for **Dlg** and **MAGI**-1 degradation.

L6 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 2
AN 2002392026 MEDLINE
DN PubMed ID: 12140759
TI Oncogenic human **papillomavirus E6** proteins target the **MAGI**-2 and **MAGI**-3 proteins for degradation.
AU Thomas Miranda; Laura Richard; Hepner Karin; Guccione Ernesto; Sawyers Charles; Lasky Laurence; Banks Lawrence
CS International Centre for Genetic Engineering and Biotechnology, Padriciano 99, 34012 Trieste, Italy.
SO Oncogene, **(2002 Aug 1)** 21 (33) 5088-96.
Journal code: 8711562. ISSN: 0950-9232.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020726
Last Updated on STN: 20020904
Entered Medline: 20020816
AB The **E6** proteins from the high-risk human **papillomavirus** (**HPV**) types have previously been shown to target a number of **PDZ** domain-containing proteins for proteasome-mediated degradation. These include the hDlg tumour suppressor and the **MAGI**-1 protein. In this study we show that high-risk **HPV E6** proteins also target the related **MAGI**-2 and **MAGI**-3 proteins for degradation. Moreover, we show that the interaction is specific to one **PDZ** domain, and that

co-expression of this domain can protect each of the full-length **MAGI** proteins from **E6**-mediated degradation. These data provide clear indicators for the potential design of compounds that could specifically inhibit the interaction of oncogenic **HPV E6** proteins with an important class of target proteins.

L6 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 3
AN 2001522961 MEDLINE
DN PubMed ID: 11571640
TI **HPV E6** and **MAGUK** protein interactions: determination of the molecular basis for specific protein recognition and degradation.
AU Thomas M; Glaunsinger B; Pim D; Javier R; Banks L
CS International Centre for Genetic Engineering and Biotechnology, Padriciano 99, I-34012 Trieste, Italy.
NC RO1 CA58541 (NCI)
SO Oncogene, **(2001 Sep 6)** 20 (39) 5431-9.
Journal code: 8711562. ISSN: 0950-9232.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200110
ED Entered STN: 20010926
Last Updated on STN: 20011015
Entered Medline: 20011011
AB It has recently been shown that the high-risk human **papillomavirus** (**HPV**) **E6** proteins can target the **PDZ**-domain containing proteins, **Dlg**, MUPP-1, **MAGI**-1 and hScrib for proteasome-mediated degradation. However, the **E6** proteins from **HPV**-16 and **HPV**-18 (the two most common high-risk virus types) differ in their ability to target these proteins in a manner that correlates with their malignant potential. To investigate the underlying mechanisms for this, we have mutated **HPV**-16 and **HPV**-18 E6s to give each protein the other's **PDZ**-binding motif. Analysis of these mutants shows that the greater ability of **HPV**-18 **E6** to bind to these proteins and to target them for degradation is indeed due to a single amino acid difference. Using a number of assays, we show that the **E6** proteins interact specifically with only one of the five **PDZ** domains of **MAGI**-1, and this is the first interaction described for this particular **PDZ** domain. We also show that the guanylate kinase homology domain and the regions of **MAGI**-1 downstream of amino acid 733 are not required for the degradation of **MAGI**-1. Finally, in a series of comparative analyses, we show that the degradation of **MAGI**-1 occurs through a different mechanism from that used by the **E6** protein to induce the degradation of **Dlg** and p53.

L6 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 4
AN 2001029726 MEDLINE
DN PubMed ID: 11077444
TI Interactions of the **PDZ**-protein **MAGI**-1 with adenovirus E4-ORF1 and high-risk **papillomavirus E6** oncoproteins.
AU Glaunsinger B A; Lee S S; Thomas M; Banks L; Javier R
CS Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX 77030, USA.
NC RO1CA58541 (NCI)
T32AI07471 (NIAID)
SO Oncogene, **(2000 Nov 2)** 19 (46) 5270-80.
Journal code: 8711562. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322

Entered Medline: 20001121

AB The oncoproteins of small DNA tumor viruses promote tumorigenesis by complexing with cellular factors intimately involved in the control of cell proliferation. The major oncogenic determinants for human adenovirus type 9 (Ad9) and high-risk human **papillomaviruses** (**HPV**) are the E4-ORF1 and **E6** proteins, respectively. These seemingly unrelated viral oncoproteins are similar in that their transforming activities in cells depend, in part, on a carboxyl-terminal **PDZ** domain-binding motif which mediates interactions with the cellular **PDZ**-protein **DLG**. Here we demonstrated that both Ad9 E4-ORF1 and high-risk **HPV E6** proteins also bind to the **DLG**-related **PDZ**-protein **MAGI**-1. These interactions resulted in **MAGI**-1 being aberrantly sequestered in the cytoplasm by the Ad9 E4-ORF1 protein or being targeted for degradation by high-risk **HPV E6** proteins. Transformation-defective mutant viral proteins, however, were deficient for these activities. Our findings indicate that **MAGI**-1 is a member of a select group of cellular **PDZ** proteins targeted by both adenovirus E4-ORF1 and high-risk **HPV E6** proteins and, in addition, suggest that the tumorigenic potentials of these viral oncoproteins depend, in part, on an ability to inhibit the function of **MAGI**-1 in cells.

L4 ANSWER 2 OF 104 MEDLINE on STN
AN 2002683177 MEDLINE
DN PubMed ID: 12444549
TI Chimaeric **HPV** E6 proteins allow dissection of the proteolytic pathways regulating different E6 cellular target proteins.
AU Pim David; Thomas Miranda; Banks Lawrence
CS International Centre for Genetic Engineering and Biotechnology, Area Science Park, Padriciano-99, I-34012, Trieste, Italy.. pim@icgeb.org.it
SO Oncogene, **(2002 Nov 21)** 21 (53) 8140-8.
Journal code: 8711562. ISSN: 0950-9232.

L4 ANSWER 3 OF 104 MEDLINE on STN
AN 2002413711 MEDLINE
DN PubMed ID: 12167343
TI Cellular steady-state levels of "high risk" but not "low risk" human **papillomavirus** (**HPV**) E6 proteins are increased by inhibition of proteasome-dependent degradation independent of their p53- and E6AP-binding capabilities.
AU Kehmeier Eva; Ruhl Heiko; Voland Britta; Stoppler Melissa Conrad; Androphy Elliot; Stoppler Hubert
CS Department of Pharmacology and Toxicology, Philipps University Marburg, Karl-von-Frisch Strasse 1, D-35033, Germany.
SO Virology, **(2002 Jul 20)** 299 (1) 72-87.
Journal code: 0110674. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200211
ED Entered STN: 20020809
Last Updated on STN: 20030304
Entered Medline: 20021106
AB The group of mucosal epithelia-infecting human **papillomaviruses** (**HPV**) can be subdivided in "low" and "high risk" **HPV** types. Both types induce benign neoplasia (condyloma), but only the infection with a "high risk" **HPV** type is causally associated with an increased risk of developing anogenital tumors. The oncogenic potential of high risk **HPVs** resides at least partially in the viral **E6** protein. The **E6** protein targets the cellular p53 protein for proteasome-dependent degradation, which is associated with the immortalizing and transforming functions of these viruses. Recently the **E6**-dependent proteasome-mediated destabilization of additional cellular proteins (E6TP1, c-myc, Bak, hMCM7, human scribble, E6AP, **MAGI**-1) has been described, but the cellular mechanisms controlling the viral **E6** protein stability itself have been so far not analyzed. In this study, we transiently expressed the **E6** genes of the high risk **HPV** type 16, the low risk **HPV** types 6a and 11, and the cutaneous epithelia-infecting **HPV** types 5 and 8 from a eucaryotic expression vector and compared the cellular steady-state levels of the expressed **E6** proteins. We demonstrated that the high risk **HPV** 16 **E6** protein possesses the lowest steady-state level in comparison to the low risk **HPV** type **E6** proteins and the cutaneous epithelia-infecting **HPV** type **E6** proteins. Inhibition of cellular proteasome-dependent protein degradation led to an increase in steady-state levels of high risk but not of low risk **E6** proteins. Analysis of functionally deficient **HPV** 16 **E6** proteins in p53 null- and p53 wild-type-expressing cell lines revealed that the cellular steady-state level of this protein is influenced neither by its p53- nor its E6AP-binding abilities.

L4 ANSWER 16 OF 104 MEDLINE on STN
AN 97471015 MEDLINE
DN PubMed ID: 9326658
TI Binding of high-risk human **papillomavirus** E6 oncoproteins to the human homologue of the Drosophila discs large tumor suppressor protein.
AU Kiyono T; Hiraiwa A; Fujita M; Hayashi Y; Akiyama T; Ishibashi M

CS Laboratory of Viral Oncology, Aichi Cancer Center, Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464, Japan.
SO Proceedings of the National Academy of Sciences of the United States of America, **(1997 Oct 14)** 94 (21) 11612-6.
Journal code: 7505876. ISSN: 0027-8424.

L8 ANSWER 3 OF 19 MEDLINE on STN
AN 2002110761 MEDLINE
DN PubMed ID: 11807220
TI Mutational analysis of the discs large tumour suppressor identifies domains responsible for human **papillomavirus** type 18 E6-mediated degradation.
AU Gardiol Daniela; Galizzi Silvina; Banks Lawrence
CS Instituto de Biologia Molecular y Celular de Rosario (IBR-CONICET), Departamento de Microbiologia, Facultad de Ciencias Bioquimicas, Suipacha 531, 2000 Rosario, Argentina.. dgardiol@fbioyf.unr.edu.ar
SO Journal of general virology, **(2002 Feb)** 83 (Pt 2) 283-9.
Journal code: 0077340. ISSN: 0022-1317.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200203
ED Entered STN: 20020215
Last Updated on STN: 20020308
Entered Medline: 20020307
AB The discs large (**Dlg**) tumour suppressor protein is targeted for ubiquitin-mediated degradation by the high-risk human **papillomavirus E6** proteins. To understand further the mechanisms behind this, a mutational analysis of **Dlg** was undertaken. This study demonstrates that an intact **PDZ** domain 2 (PDZ2) on **Dlg** is necessary for the ability of **E6** to bind and degrade **Dlg**. However, additional residues within the amino-terminal portion of **Dlg** are also required for optimal **E6** activity. Stable cell lines expressing different **Dlg** mutants were also established and these confirm that **Dlg** is regulated intrinsically by the proteasome in the absence of **E6**; however, in this case, the sequences responsible for regulating **Dlg** stability lie predominantly within PDZ2. These results suggest that there are at least two mechanisms for regulating **Dlg** protein stability and that the pathways used by **E6** are not necessarily the same as those used in the cell in its absence.

L8 ANSWER 10 OF 19 MEDLINE on STN
AN 2000162315 MEDLINE
DN PubMed ID: 10698489
TI **HPV** E6 targeted degradation of the discs large protein: evidence for the involvement of a novel ubiquitin ligase.
AU Pim D; Thomas M; Javier R; Gardiol D; Banks L
CS International Centre for Genetic Engineering and Biotechnology, Trieste, Italy.
NC ROI CA58541 (NCI)
SO Oncogene, **(2000 Feb 10)** 19 (6) 719-25.
Journal code: 8711562. ISSN: 0950-9232.

L8 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:131285 CAPLUS
DN 128:165635
TI Binding of viral oncogenic proteins and **PDZ** domains of cellular proteins
AU Hiraiwa, Atsuro; Ishibashi, Masahide
CS Sch. Med., Nagoya Univ., Nagoya, 466-8550, Japan
SO Tanpakushitsu Kakusan Koso **(1998)**, 43(3), 237-243
CODEN: TAKKAJ; ISSN: 0039-9450
PB Kyoritsu Shuppan
DT Journal; General Review
LA Japanese

AB A review with 24 refs. on binding of human **papillomavirus** **E6** protein with the **PDZ** domain of hDLG (human homolog of Drosophila disks large tumor suppressor protein) in relation to transforming activity. Binding of hDLG with E4ORF1 protein of adenovirus or Tax protein of HTLV-1 is also described.

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DATE: Thursday, July 14, 2005

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	DB=USPT; PLUR=YES; OP=OR		
☐	L18	2000	41
☐	L17	L14 and isolated with (protein or $peptide) same (assay or method or screen$)	298
☐	L16	L14 and isolated with (protein or $peptide)	360
☐	L15	L14 and L13	57
☐	L14	(screen$ or identif$) with (inhibit$ or drug or antagon$) same (peptide-peptide or protein-protein) near4 (interact$ or binding)	442
☐	L13	L12	523
	DB=PGPB,USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=OR		
☐	L12	2000	548
☐	L11	L10 and (inhibit$ or drug or antagon$) near6 (interact$ or binding)	8487
☐	L10	(peptide-peptide or protein-protein) near4 (interact$ or binding) and (screen$ or identif$) with (inhibit$ or drug or antagon$)	9531
☐	L4	l1 and l2	122
☐	L3	l1 and l2L2	0
☐	L2	(peptide-peptide or protein-protein) near4 (interact$ or binding)	12277
☐	L1	drug adj screening same (cellular or cell-based or cell adj based) near4 assay	921

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DATE: Thursday, July 14, 2005

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=OR	
☐	L5	l1 and (HPV or papillom$ or HPV) same (MAGI-1 or MAGUK or membrane adj associated adj guanylate adj kinase adj interacting near3 1)	6
☐	L4	L3 and l2	11
☐	L3	l1 and (MAGI-1 or MAGUK or membrane adj associated adj guanylate adj kinase adj interacting near3 1)	28
☐	L2	(papillomavir$ or HPV or E6) same (PDZ or DLG or MAGI-1 or MAGUK or membrane adj associated adj guanylate adj kinase adj interacting near3 1)	20
☐	L1	(papillomavir$ or HPV or E6) and (PDZ or DLG or MAGI-1 or MAGUK or membrane adj associated adj guanylate adj kinase adj interacting near3 1)	126

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- Click on query # to add to strategy

Search	Most Recent Queries	Time	Result
#8	Search **MAGI* AND (HPV or E6)**	13:09:53	15
#7	Search **MAGI* AND (HPV or E;)**	13:09:43	547

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